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Development of decision tools to assess the migration from plastic materials in contact with food

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Abstract

Testing the specific migration limits of all substances intentionally added to polymer material according to European Union (EU) regulation is a tedious and expensive task. Although mathematical modeling offers an interesting alternative, it can significantly overestimate the migration in situations, which are strongly conservative due to significant uncertainty in transport properties. In addition, its application is of little use for end-users or enforcement laboratories, which do not have access to the formulation. This paper revises the paradigm of migration modeling by combining modeling with deformation experiments and iterative modeling in the framework of decision theory. The complete approach is illustrated for polyolefins in contact with 50% ethanol for eight typical migrants, including hindered phenolic antioxidants and low molecular weight surrogates. Results from a French ACTIA

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project on the identification of formulation fingerprints and on the prediction of partition coefficients with alcoholic and aqueous stimulants is described. When the true migration was close but still lower than the limit of concern, the proposed compact decision tree, including up to four sources of uncertainty, showed that the chance of demonstrating compliance was about 3:4 in the presence of one source of uncertainty, whereas it fell below 2:4 and 1:4 with two and three sources of uncertainty respectively. The recommendations for further food packaging safety surveys and future developments are discussed.

Key words: food contact materials, migration modeling, compliance testing, sanitary survey.

Introduction

For the last three decades, consumer exposure to chemicals from food packaging materials has attracted much public attention and interest of European regulatory authorities. Thus, although the EU regulation is still in a consolidation phase, 502 substances (including 230 monomers and 272 additives) among the 937 which are positively listed in EU directives on plastics in contact with food (European Commission, 2008), are subjected to specific migration limits (SML) due to toxicological concern. The recent authorization of substances not belonging to the positive list, when they are located behind one or more layers, the so-called functional barrier, which prevents their migration into foods or food simulants above a detectable level (European Commission, 2007), complicated the assessment of compliance testing and requirements of traceability (European Commission, 2004). The introduction of modeling in directive 2002/72/EC (European Commission, 2002) as an alternative to time consuming migration testing was an appropriate response to the increasing sophistication of plastics materials on the market including multilayer materials, active or intelligent packaging, recycled polymers, nanocomposites... Despite significant collaborative work on

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3 48 the collection of diffusion coefficients (Begley *et al.*, 2005; Dole *et al.* 2006), the whole
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5 49 approach remains highly semi-empirical and insufficiently described in the literature
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8 50 according to the application context. Most of studies are focused on demonstrating that
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10 51 predictions based on worst-case scenarios overestimate the real migration (Franz and Welle,
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12 52 2008). As a result, in the current framework, either worst-case modeling does demonstrate the
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14 53 compliance or migration testing must be performed. In practice, the highly asymmetric
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16 54 know-how and information along the food-packaging chain from the producer to consumer is
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18 55 responsible for considerable uncertainty on the consumer side, which lessen drastically the
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20 56 interest of modeling for end-users, enforcement authorities (Petersen *et al.* 2005) and
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22 57 authorities responsible for food safety surveillance.
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27 58 The very low utility of current predictive approaches, expressed as a probability to
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29 59 demonstrate the compliance, is illustrated as a decision diagram in Figure 1, where a
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31 60 probability of acceptance is associated with each alternative. Reference probabilities, gathered
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33 61 in Table I, were assigned according to the expertise obtained at the Laboratoire National de
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35 62 métrologie et d'Essais (LNE) and at the Institut National de la Recherche Agronomique
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37 63 (INRA). The current utility for a national reference laboratory as LNE is estimated lower than
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39 64 3:1000 for most of monolayer cases. The main limiting factors are the identity of substances
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41 65 and their amounts in the starting materials. Additional limitations arise from the lack of
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43 66 realistic estimates of transport coefficients (diffusion coefficients and partition coefficients) in
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45 67 the conditions of storage. The combined effect of several sources of uncertainty including on
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47 68 composition and transport coefficients has been studied extensively for monolayer materials
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49 69 (Vitrac and Hayert, 2005) and extended to multilayer materials and multimaterials (Vitrac and
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51 70 Hayert, 2007) via a stochastic description of the contamination of food and an interval
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53 71 approach, respectively. They showed that the expected utility collapsed rapidly as soon as
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55 72 more than two sources of uncertainty were combined. Full modeling approaches independent
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on specific experiments has been applied on finished food products on the market (Vitrac *et al.*, 2007) and on consumer exposure (Vitrac and Hayert, 2007) only in rare occasions where a significant expertise on physicochemical properties of packaging materials was available.

This paper proposes to revise the paradigm of migration modeling by introducing modeling along with deformation experiments and refined prediction scenarios, recently made available. The main objective was to combine several rapid experimental and numerical techniques to improve the expected utility value up to 1:3 (Table I), in order to justify the additional costs induced by modeling (software licenses, training...). The final approach will be integrated in an expert system developed by INRA including databases and simulation tools. In this new framework, the issue is not to minimize the deviation between the predicted value and the real one, but determining the fastest decision path among possible alternatives to demonstrate the compliance in the first place. The demonstration relies either on a predicted value lower than SML or to a maximum initial concentration value in the polymer (MIC), acknowledged by the supplier to be higher than the true amount (Figure 1). The proposed four steps algorithm is particularly comprehensive for monolayer materials as few input parameters, denoted x_i , and including initial concentrations, partition coefficients and diffusion coefficients, are involved:

- Step 1: finding the most influencing set of inputs, $X = [x_1 \ x_2 \ ...x_n]$ for the considered conditions of migration (food packaging geometry, contact time and temperature...).
- Step 2: finding the optimal set x° , which leads to migration = SML (idem with MIC).
- Step 3: for all inputs in the set, finding all conditions " $x_i < x_i^\circ$ " or " $x_i > x_i^\circ$ " to guarantee migration < SML.
- Step 4: check whether all conditions are likely according to values available in databases, additional modeling or to experiments.

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3 98 The first step is the most critical because the number of influencing inputs, n , and their
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5 99 identities are not a priori known. Our objective was to analyze all four steps for polyolefins in
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8 100 contact with 50% ethanol as simulant of dairy products (European Commission, 2007). This
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10 101 situation was of significant concern as polyolefin materials represent nearly one third of all
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12 102 food packaging applications and currently no specific guidance exists to predict the migration
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14 103 in such a food simulant. Additional interest in such semi-crystalline materials was triggered
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16 104 by the recent validation of several alternatives to conventional migration testing.
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18 105 Overestimates (Begley *et al.*, 2005) and likely estimates (Vitrac *et al.*, 2006) of diffusion
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20 106 coefficients have been published for all substances, which do not cause blooming effects. The
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22 107 French national project ACTIA RA 0522 “decision tools for compliance testing” (ACTIA,
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24 108 2005) contributed to generate missing steps in the predictive approach of the migration from
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26 109 polyolefins starting from the diagram depicted in Figure 1: i) rapid deformation of materials
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28 110 from Fourier Transform Infrared spectroscopy (FTIR) absorption spectra of polymer extracts
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30 111 (Gillet *et al.*, 2009a), ii) prediction of partitioning between polyolefins and most simulants
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32 112 (alcohols, water and water-ethanol mixtures) from molecular simulations of molecular pair
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34 113 interactions (Vitrac and Gillet, 2008; Gillet *et al.*, 2009b and 2009c). The importance of
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36 114 deformation to identify possible migrants and their extent has been already discussed in the
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38 115 conclusions of the EU AIR research program CT94-1025 (Feigenbaum *et al.*, 2002). For
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40 116 polymer additives comprising several repeated chemical patterns, e.g. di-tert-butylphenol in
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42 117 hindered phenolic antioxidants, FTIR offers additional worst-case scenarios based on an
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44 118 equivalent amount patterns, considered as high diffusing individual molecules. The direct
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46 119 calculation of activity coefficients at atomistic scale for both flexible migrants and hindered
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48 120 migrants in various food simulants and in polyolefins widens dramatically the range of
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50 121 applicability of modeling for monolayer and multilayer materials (Gillet *et al.*, 2009b; Gillet
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52 122 *et al.*, 2009c; Vitrac and Gillet, 2008; Vitrac and Gillet, 2009). As the approach was validated

in more than 51 different conditions and did not require any fitting procedure, it would replace advantageously both rough estimations suggested in the “practical guide” to European Directives (European Commission, 2003) and the semi-empirical group contribution devised for the partitioning of volatile substances (Baner and Piringer, 1991). Besides, direct calculations provided two important insights at molecular scale, which were underestimated in previous works (Gillet *et al.*, 2009b). On one hand, additives comprising a repeated pattern have a higher chemical affinity than their constitutive patterns for simulants. This entropic effect, which does not depend on chemical composition effects, was related to the increased number of micro-configurations to recreate simulant-simulant interactions (e.g. hydrogen bonding) when a large guest molecule was inserted among smaller host ones. The practical consequence is that the partitioning of large additives cannot be extrapolated from volatile substances. On the other hand, strong deviations from ideality in water-ethanol mixtures were found to be responsible for highly non-linear variations of partitioning with the volume fraction in ethanol, and where in contradiction from prior extrapolations in pure water. The practical consequence is that the lowest chemical affinity for the simulant is expected to be obtained with 20%-30% ethanol rather than in pure water Gillet *et al.* (2009c).

The paper is organized as follows. The first section details the methodologies, assumptions and scenarios to assess the compliance according to the decision tree depicted in Figure 1 and the proposed four steps algorithm. As a quantification of the initial amount may be required, a fast extraction technique under pressure was compared with the conventional reflux method on a typical high density polyethylene (HDPE). Eight typical migrants of polyolefins were particularly considered. The photo-initiator used in printing inks, 2-isopropylthioxanthone (2-ITX), was included because it was recently found in several food products including dairy ones in spite of not being authorized in EU (Bagnati *et al.*, 2007; Sun

et al., 2007; Rothenbacher *et al.*, 2007). The main experimental and simulated results are presented in the second section. Biases due to possible incomplete extractions of semi-crystalline polymers, which are insoluble in solvents, were tabulated according to the number of extraction steps as suggested by Choller *et al.* (2003). The effect of combined sources of uncertainty was analyzed by ranking all prediction scenarios according to their ability to demonstrate the compliance and according to the number of uncertain inputs. The main interest of the approach is that the typical generated diagrams can be used to extrapolate the effect of uncertainty for migrants different from those studied by simple geometric constructions. The findings and provides recommendations for its generalization in good manufacturing practices and quality auditing purposes are summarized in the last section.

Materials and methods

Tested substances

Tested substances are listed in Table II. They were chosen to be representative of most technological functions in polyolefins. Irganox 1330 and Irganox 3114 were proposed as typical phenolic hindered antioxidants including a repeated chemical pattern. As they include three BHT patterns, they can be easily mistaken for dispersed BHT molecules in FTIR spectroscopy, with an equivalent concentration assessed three times higher than the true one. Erucamide is an unsaturated long chain carboxylic acid amide used as slip agent or lubricant in plastic films. At concentrations above $10^3 \text{ mg}\cdot\text{kg}^{-1}$ in polyolefins, it is only partly compatible with polyethylene (Gillet *et al.*, 2009c), its migration does not obey to Fickian diffusion and migration modeling cannot be applied. As a result, it was only used in

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3 170 extraction experiments as a prototype of substance poorly dispersed in polyolefins. Two
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5 171 typical low molecular weights surrogates, which are not intentionally added substances into
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8 172 plastics, were also included: 2-ITX and diphenylmethane. The latter was introduced as
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10 173 partitioning data have already been published by Baner and Piringer (1991).
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15 175 *Evaluation of extraction methods*

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17 176 Extraction methods were evaluated on HDPE films formulated with Irganox 1076, Irgafos
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19 177 168 and Erucamide. Dried polymer flakes were formulated during a first extrusion step prior
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22 178 to final processing at a semi-industrial scale. Both extrusions were performed at 200°C in a
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24 179 bi-screw extruder (model BC-21 Clextral, France) and the material was finally calendered as
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26 180 0.15 m wide ribbons. The final density and the crystallinity were of 940 kg·m⁻³ and 70 %
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29 181 respectively, with a melting point of 136°C. Plastic additives were provided by CIBA (Basel,
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31 182 Switzerland) except for Erucamide, which was obtained from CRODA (Vimodrone, Italy).
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33 183 Raw HDPE was obtained from ATOCHEM (Paris, France).
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36 184 Two common extraction methods were considered: a conventional 40 h reflux extraction
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38 185 method in dichloromethane and a 40 min pressurized solid-liquid extraction (model ASE 200,
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41 186 Dionex, USA) in a 75:25 v/v mixture of isopropanol-dichloromethane at 105°C and 10.3
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43 187 MPa. The latter conditions were similar to ones described by Coulier *et al.* (2005) and were
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45 188 applied to 600 mg of samples mixed with sand in 11 ml extraction cells. Two static cycles of
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48 189 15 min each were applied to achieve complete extraction. To prevent the degradation of
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53 190 additives during extraction, 100 µL·L⁻¹ of tri-ethylphosphite (Sigma-Aldrich, USA) was
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191 added to solvents for both methods.

Determination of concentrations in extracts was done by high-performance liquid chromatography (HPLC) with diode array and evaporative light scattering detection. The HPLC system consisted in a Waters 717plus autosampler, a Waters 600 controller equipped with a thermostatted column compartment and an in-line degasser AF (Waters, USA). The protocol described by Garrido-López (2005) was used. Separation was achieved on a Xterra C8 column (150mm×3.0mm; 5µm particles; Waters , USA) operated at 60°C.

Migration modeling

Migration modeling was performed under the same assumptions described by Vitrac and Hayert (2006) and by Vitrac *et al.* (2007) for similar applications. Migration in food or in a food simulant was assumed to be one-dimensional without any reaction and mass losses with surroundings. The material was considered to be homogeneous and the relaxation of polymer chains was assumed unaffected by the desorption process. The concentration profile in substance *i*, $C_i(Fo,x)$, along the packaging thickness, with SI units in $\text{kg}\cdot\text{m}^{-3}$, evolved

therefore with the dimensionless diffusion time, denoted Fo , as:

$$\frac{\partial C_i(Fo,x)}{\partial Fo} = \frac{\partial^2 C_i(Fo,x)}{\partial x^2} \tag{1}$$

Where $Fo = D_{i,p} \cdot t / l_p^2$ and x is the dimensionless position between 0 and 1 within the film.

$D_{i,p}$ is the diffusion coefficient with SI units in $\text{m}^2 \cdot \text{s}^{-1}$; l_p is the packaging thickness and t is

the contact time. Only a pervious contact is assumed on food side, at $x=1$:

$$\left. \frac{\partial C_F}{\partial Fo} \right|_{Fo} = - \left. \frac{\partial C_i}{\partial x} \right|_{x=1, Fo} = Bi \cdot [K_{i,F/P} \cdot C_i(x=1, Fo) - C_F(Fo)] \quad (2)$$

where Bi is the mass Biot number assigned to 10^3 to prevent a significant mass transfer resistance at the interface, as the liquid simulant was stirred.

$K_{i,F/P} = C_{i,F}(Fo \rightarrow \infty) / C_{i,p}(x=1, Fo \rightarrow \infty)$ is the partition coefficient between the food product or food simulant, denoted F , and the packaging material, denoted P . The concentration in food or in food simulant, $C_F(Fo)$, was obtained from the mass balance $t=0$ and t by assuming a uniform initial concentration profile equal to $C_{i,p}^0$:

$$L_{F/P} \cdot C_F(Fo) = C_{i,p}^0 - \int_0^1 C_i(x, Fo) \cdot dx \quad (3)$$

where $L_{F/P} = V_F / (A \cdot l_p)$ is the volume dilution ratio. V_F and A are respectively the volume of F and the contact surface area between P and F . Equations 1-3 were integrated in time using a finite volume technique documented and implemented online in QSPR-MS tools of the Safe Food Packaging Portal (INRA 2008). All simulations results were exported as datasheets to be further interpreted.

Migration scenarios

Ten scenarios with different sources of uncertainty were considered for five additives as plotted in Figure 2. For each quantity X required for modeling, two values were considered: a likely value $\bar{X}$ and a robust overestimate X^+ such that $\bar{X} < X^+$. The corresponding values are gathered in Table III for each substance and in Table IV for each scenario. A similar $\bar{D}_{i,p}$ value was assigned to Irganox 1330 and Irganox 3114 as they had a very similar chemical structure and as the expected difference is lower than the common experimental error as assessed in (Vitrac *et al.* 2006). $\bar{K}_{i,F/P}$ values were calculated in the framework of a generalized Flory-Huggins theory at atomistic scale as discussed in Vitrac and Gillet (2008) and in Gillet *et al.* (2009b and 2009c). Desorption was assumed to occur in water-ethanol (50:50 v/v) to simulate a contact with a dairy product (European Commission 2007). As a possible worst case of packaging materials in contact with a dairy product, additives were assumed to be used in a rigid container of 200 μm thickness and in contact with a low volume of food of 100 mL. The conditions of test corresponded to a contact of 10 days at 40°C. By contrast, low molecular weight contaminants were assumed to be located in thin 50 μm liner in contact with a product of 1 L. To simulate more realistic conditions in the latter case, a contact with a dairy product at 4°C during 90 days was assumed.

The scenarios numbered from 1 to 8 were located at the vertices of a cube (Figure 2). The face 1,4,7,3 corresponded to uncertainties on transport properties. The opposite face 2,6,8,5 combined in addition uncertainty on composition, $C_{i,p}^0$. In absence of a transport property, a robust overestimate was used instead. As no recommendation has been specifically proposed for 50% ethanol used as simulant, an upper bound of 10^3 was chosen for $K_{i,F/P}^+$ instead of the unitary value recommended for simulant D (olive oil) in the “Practical Guide” (European Commission 2003) as extreme worst case. This choice was consistent with experimental $K_{i,F/P}$ values found higher than 1 between polyolefins and ethanol (Vitrac *et al.* 2007, Gillet *et al.* 2009c). As detailed in table II, in absence of data on initial concentrations for migrants used

as additives (Irganox 1330, Irganox 3114, BHT), maximum values recommended by the providers were used. For low molecular weight contaminants (2-ITX and diphenylmethane), concentrations in agreement with the extensive study of Rothenbacher *et al.* (2007) were used.

Scenarios 9 and 10 were special cases where the identity of the migrant *i* was unknown. In this work, they were applied to phenolic antioxidants similar to those previously studied (Irganox 1330, Irganox 3114 and BHT) but for which only an estimate of the concentration in di-tert-butylphenol (BHT pattern) was assumed to be known, as detailed in Table IV. This situation was consistent with a concentration determination by FTIR (Gillet *et al.*, 2009a).

Results and discussion

Extraction yields

A list of substances, which may migrate from the contact material to the food, is conventionally required before starting any assessment of specific migration limits. This approach is well suited for substances, which are intentionally added to materials in contact with food. This information is obtained either by partial disclosure of confidential information or by a deformation step. For practical cases taken in consideration by the Laboratoire National d'Essais in France, the formulation is transmitted for less than 5 % of tested samples (Table I). As a result, deformation appears currently as the most robust approach to start the decision tree depicted in Figure 1. To be cost-efficient, this additional step must be rapid and predictive. The difficulty arises with semi-crystalline materials such as polyolefins, which cannot be dissolved in most of solvents below their melting point. Figure 3 presents the estimated concentration in *P* after successive extractions during a long-term extraction by reflux (extraction time 48 h) and using a pressurized cell (extraction time 40 min). The data

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were obtained for two typical antioxidants, Irganox 1076 and Irgafos 168, well dispersed in the bulk and a slip agent, Erucamide, mainly located at the external surface of *P*.

Differences between methods and substances (including 3 extractions×3 concentrations measurements) were almost insignificant. As only leaching was required to extract Erucamide from HDPE, the extraction was complete in one step. For additives dispersed in the bulk, 95 % extraction was reached after the first step. The bias related to a single extraction was therefore minimal. Although the extraction bias (systematic error) could be corrected with the extraction yield, the experimental error (random error) was much higher. The overall relative experimental error was assessed up to 20 % and did not decrease with the considered number of extraction steps, since the extracted amounts were cumulated and not averaged. The magnitude of the extraction error was directly correlated to the accuracy of sampling and concentration measurements.

Migration kinetics

Figure 4 plots the dimensionless kinetics corresponding to the most complete scenario (i.e. with the lowest uncertainty), ranked 1 in Figure 2, for three antioxidants initially included in a 200 µm thick film in contact with 50% ethanol ($L_{F/P}=50$) at 40°C. The dimensionless diffusion time corresponding to a conventional contact time of 10 days at 40°C, denoted F_{O10} , is also depicted. Although most of decision-makers would not start with this scenario, it is particularly useful to illustrate the migrant based reasoning. Diffusion behavior of BHT was highly distinct of additives including several BHT patterns with a F_{O10} value close to 6

296 against a value of $4 \cdot 10^{-2}$ for Irganox 1330 and Irganox 3114. Concentration values at

297 equilibrium, $C_{i,F}^{(F_0 \rightarrow \infty)}$, given by the overall mass balance defined in Equation 4, were also
298 highly different:

$$299 \quad C_{i,F}^{(F_0 \rightarrow \infty)} = \frac{1}{L_{F/P} + 1/K_{i,F/P}} \cdot C_{i,P}^0 \quad (4)$$

300 As a same dilution ratio, $L_{F/P}$, and a same initial concentration, $C_{i,P}^0$, were applied to all
301 migrants, the differences in calculated migration rates were only related to partitioning
302 between HDPE and 50% ethanol, $K_{i,F/P}$ used as input. Despite all migrants consisted in the
303 repetition of same BHT pattern, their chemical affinity for 50% ethanol varied significantly
304 with their size. This effect has been extensively studied in Gillet *et al.* (2009b and 2009c) and
305 has been proposed to explain the relative high chemical affinity of large additives for mixtures
306 consisting in much smaller molecules. Similar considerations are detailed by Fill and
307 Bromberg (2003). Accordingly, the effect of solute size on $K_{i,F/P}$ was related to a much higher
308 dispersion of chemical interactions between the migrant and the simulant when the migrant
309 was larger. Indeed, a large molecule as Irganox 3114 consisting in 3 BHT patterns exposed a
310 much lower specific surface to simulant than a single BHT molecule and consequently
311 perturbed less the cooperative network of hydrogen bonds in water-ethanol mixtures. It is
312 underlined that the current approach neglects possible reactions, which could reduce the size
313 of migrants and which could modify accordingly the chemical affinity of fragments for the
314 simulant.

In detail, the migration of large additives, Irganox 1330 and Irganox 3114, was controlled by both the migrant chemical affinity for 50% ethanol (which favors the migration comparatively to BHT) and by the limiting diffusion in the film. . The uncertainty effects were however not symmetric. As illustrated in Figure 4b, concentrations of Irganox 1330 and 3114 in simulant were greater than 40 % of their equilibrium values, e.g. maximum possible concentration in simulant. Overestimating diffusion coefficients would therefore increase the concentration in food simulation at a maximum by a factor $1/0.4=2.5$. In contrast, overestimating the partitioning by several orders of magnitude might lead to a complete extraction, that is $1/50$ the initial concentration, that is overestimating the expected migration by one order of magnitude (Figure 4a).

It is worth noting that such a very low partitioning (Table III) with the simulant requires a particular care in the writing of the boundary condition (Equation 2) and in the resolution of the complete set of transport equations. It is expected that the requested time to reach the equilibrium is lower when the chemical affinity is very low for F . Simply explained, the equilibrium was reached all the more rapidly when the amount of migrant to be desorbed to reach the equilibrium was lower. In the absence of chemical affinity of the simulant, the macroscopic equilibrium would be thus obtained instantaneously as soon as a single molecule would have left the polymer. These features, which may appear counter-intuitive, are discussed by Vitrac and Hayert (2006).

The practical consequence was that the mis-identification in FTIR of Irganox 1330 as BHT, with a three times higher molar concentration (note that the mass concentration would remain unchanged), would not be necessarily a worst case as the affinity of Irganox 1330 for the simulant would be also higher.

Sensitivity diagrams to uncertainty

Introducing simultaneously a significant amount of uncertainty for the diffusion coefficient and partition coefficient, as it could be in practice, complicates arriving at clear conclusions regarding the possible exceedance of a given threshold. The effects of combined variations in $K_{i,F/P}$ and $D_{i,P}$ values, corresponding to Figure 4, are illustrated as isocontours of $10^3 \cdot C_{i,F}^{(Fo)} / C_{i,P}^0$ in Figure 5 for two dilution ratios: $L_{F/P}=50$ and $L_{F/P}=83$. These ratios matched the conventional assumption used in conservative consumer exposure assessment in EU (European Commission 2002): 1 kg on food in contact with 6 dm² of packaging material. In Figure 5, the values corresponding to scenarios numbered from 1 to 8 (see Table IV) are plotted at the vertices of a rectangle. The extents of variations represent the effects of overestimations when one or two input values were missing and when strong overestimates were used instead (see Table III).

For a small migrant as BHT, equilibrium was reached in less than two days so that only uncertainty on partitioning was able to change the concentration in food simulant after 10 days. By choosing $K_{i,F/P}^+$ (scenarios 3,5,7,8), the extraction was almost complete and the concentration in simulant was solely controlled by the maximum permitted concentration in HDPE. The overestimation factor reached up two decades. The behavior was opposite for large antioxidants and their migration rates were almost independent of partitioning. The isocontours appeared therefore mainly parallel to $K_{i,F/P}$ axis with a maximum overestimation factor of 5. According to Equation 4, it is worth to notice that decreasing $K_{i,F/P}^+$ from 1000 down to 1 (worst case recommended in “practical guide” (2003)) did not change previous conclusions as $L_{F/P}$ values higher than 10 led to almost complete extraction for any $K_{i,F/P}^+ \geq 1$.

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3 362 $L_{F/P}$ introduced only some additional effects. They were related to two complementary
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5 363 contributions: i) lowering the effect of a poor chemical affinity for simulant at high $L_{F/P}$
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7 364 values and ii) increasing the dilution of the amount of migrated substances. Depending on the
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12 365 units used to express the specific migration limit (SML), in $\text{mg}\cdot\text{dm}^{-2}$ of packaging or $\text{mg}\cdot\text{kg}^{-1}$
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22 366 of packaging, the one or the other led to a more conservative assumption. As we expressed
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26 367 SML in $\text{mg}\cdot\text{kg}^{-1}$, $L_{F/P}=50$ was chosen in the remainder of the work as a worst case
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36 368 assumption. The conventional assumption 1 kg in contact with 6 dm^2 would lead to a
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38 369 concentration in food simulant down to twice lower.
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43 371 The effect of cumulating up to three sources of uncertainty made the utility of some
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45 372 scenarios questionable according to the expected migration limit of concern (SML or
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47 373 detection limit). To generate a practical sensitivity diagram depicting all combined sources of
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50 374 uncertainty, a simplified descriptor, derived from Equation 2, $Fo_{10} \cdot K_{i,F/P}$ was used instead of
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52 375 isocontours. For low molecular weight contaminants with a contact time of 90 days (Table
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55 376 III), a similar descriptor was proposed: $Fo_{90} \cdot K_{i,F/P}$. Values of $C_{i,F}^{(Fo=Fo_{10}, Fo_{90})}$ against the previous
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58 377 criteria are plotted in Figure 6 for $\bar{C}_{i,P}^0$ and $(C_{i,P}^0)^+$. Confidence intervals caused by
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60 378 uncertainties on transport properties, $\bar{K}_{i,F/P}$ and $\bar{D}_{i,P}$, are also presented to highlight that the

decision of compliance should not be taken necessarily at the predicted value but should include an additional safety margin.

Combining several sources of uncertainty showed that the hierarchy of scenarios to demonstrate the compliance was not intuitive as it depended on the considered case.. Scenarios involving $K_{i,F/P}^+$ values (3,5,7,8), as generally recommended for migration modeling, were able to demonstrate the compliance only when the migration limit was as high as the overall migration limit in EU regulation, 60 mg·kg⁻¹, that is for Irganox 1330. By

contrast, refined scenarios 1,2,4,6 involving at least one likely transport properties were always applicable to demonstrate compliance. Irganox 3114 and DPM were special cases, where compliance could not be determined when more than one source of uncertainty was included.

Decision diagrams in MIC

The usability of previous sensitivity diagrams by end-users, having not access to the initial formulation of their materials, was improved by replacing the concentration in food simulant by the equivalent maximum concentration in the packaging material, *MIC*, which matches the limit of concern. It was calculated as:

$$MIC = \frac{C_{i,P}^0}{C_{i,F}^{(Fo)}} \cdot \text{limit of concern} \quad (5)$$

MIC values are more practical as they can be calculated *a priori* for a given food packaging application and they can be compared subsequently with formulation data derived from general manufacturing practices or from a partial formulation disclosure (Figure 1). The

interesting feature is that the provider needs only to acknowledge that it uses the substance at a lower concentration than *MIC*. To make robust conclusions, the uncertainty associated to each *MIC* estimates must be accounted. *MIC* values corresponding to Figure 6 are plotted in Figure 7 in increasing order. When implemented as decision diagram, each bin represents a condition node: is the initial concentration higher than the value above each bin? If the answer is yes, the question must be repeated with the next bin on the right. If the answer is no, the compliance is demonstrated. For large additives, the *MIC* values were progressively increasing as the migration model was sensitive to all sources of uncertainty. For low molecular weight contaminants and additives, changes between values were most abrupt. Ordering scenarios *a priori* guaranteed the decision-maker that acquiring new information will improve the decision. A strict improvement is obtained by merging scenarios with similar values. As it is physically expected, $\bar{K}_{i,F/P}$ was the most valuable information for small migrants while it was $\bar{D}_{i,P}$ for large additives including a repeated pattern.

Decision diagrams for phenolic antioxidants mistaken with BHT

When the identity of the substance was not known as it might occur in FTIR deformation, a large molecule (in this work a large hindered phenolic antioxidant) was replaced by much smaller one (BHT). This approximation suited particularly for Irganox 1330 and Irganox 3114. Nevertheless two additional difficulties appeared: the initial concentration was expressed in equivalent concentration in BHT patterns and the limit of concern was assumed to be the SML of BHT. The reliability of such assumptions to demonstrate the compliance is depicted in Figure 8. As the SML of BHT was much lower than the one of real additives, the approximation guaranteed a conservative decision limit. By introducing the expected transport properties of BHT, $\bar{D}_{BHT,P}$ and $\bar{K}_{BHT,F/P}$, and an equivalent concentration in BHT pattern, the predictions of scenarios 9 and 10 were close to those of

scenarios 1 and 2 respectively (Figure 5). As a result, the compliance could be demonstrated easily with scenario 9 and 10.

The proposed approximation seemed valid when BHT replaces molecules based on the repetition of several BHT patterns. It should not be generalized to any series of additives. A more general estimate based on $D_{BHT,P}^+$ and $K_{BHT,F/P}^+$ was tested and plotted as scenarios 9' and 10' in Figure 8. As it led to equivalent MIC values lower than 200, it was not suitable for antioxidants, which are conventionally used at concentrations much higher.

Shortest paths to demonstrate the compliance

From the point of view of decision-maker, the dependence diagram depicted in Figure 2 should be started in the reverse order with the lowest knowledge level. For antioxidants, it could be started with scenarios 9 and 10 as a homologous molecule was available. For other molecules, it should be started with the scenario 8. The best scenario was the one, which made it possible to demonstrate the compliance and was connected with shortest path length (decision path length) to the initial scenario. In other words, the optimal scenario should minimize the extent of additional information necessary to demonstrate the compliance.

Previous figures 5-6 cannot be used directly to determine the shortest path length as they focus on the values of physicochemical properties instead of on the amount of available information. In practice, the lengths of all possible paths (8) were read in Figure 2, they did not depend on the considered substance or on the considered problem. The efficiency of each corresponding scenario (ability to demonstrate the compliance) depends both on the considered case, e.g. substance, and on the decision limit value. In order to derive almost self-similar diagrams, i.e. reusable for other applications, where the shortest distance can be easily read, all scenarios were ranked according to their equivalent decision path length and plotted

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3 450 in Figure 9 as concentrations normalized according to the considered SML. Starting from the
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5 451 left, the shortest path length was consequently defined as the first abscissa with a normalized
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7 452 concentration lower than 1. Except when the SML was as high as the global migration limit
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9 453 (Irganox 1330), a path of length 4 was required, which indicated that no more than two
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11 454 sources of uncertainty could be combined. On one hand, it could be argued, as a rule of
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13 455 thumb, that when partial formulation disclosure is not accepted or available, at least one
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15 456 transport property must be known with enough accuracy. On the other hand, when the initial
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17 457 concentration is available, conventional overestimates, although inaccurate, are expected to be
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19 458 able to demonstrate the compliance not in all cases but with a significant expectation, between
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27 460 For polyolefins (one third of total food contact applications), the current state of the art
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29 461 suggests that scenario 2 and possibly scenario 1 should be nearly available for all practical
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31 462 cases, while minimizing the risk of false negative (considered as “not able to demonstrate the
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33 463 compliance” when it is compliant). In addition, the risk of false positives would be very low
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35 464 while appropriate safety margin on likely transport properties are included in the decision.
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41 466 **Conclusions and future prospects**

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43 467 This paper addresses a general framework to combine migration modeling and experiments
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45 468 into the same decision tool to demonstrate the compliance of thermoplastics materials in
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47 469 contact with food with regulatory limits. The objective was to select the necessary
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49 470 experiments and simulation scenarios among several alternatives to make a decision: “it is
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51 471 compliant” or “the compliance cannot be demonstrated with this approach”. In comparison to
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53 472 conventional approaches used in migration modeling, the ambition was neither to assess the
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55 473 real migration nor to overestimate all uncontrolled factors but to dramatically increase the
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usability of modeling-based compliance testing. The improvements consisted mainly in designing an end user-oriented approach, which was:

- more efficient (more robust, it takes less time to accomplish the demonstration, it requires fewer assumptions, formulation disclosure is not systematically required...);
- easier to learn (based on simple diagrams, include a robust physical reasoning based in particular on minimal number of dimensionless quantities);
- more satisfying to use (the method toggles when required from empirical models of transport properties to more sophisticated ones based on a molecular simulation).

The method was tested in complicated cases involving the migration of low molecular weight contaminants and hindered phenolic antioxidants into the simulant proposed for dairy products, 50% ethanol, for which the possibilities of modeling had not yet been examined. Although the current results might find an application in the previous 2-ITX crisis, the finality was mainly methodological. All ten scenarios incorporating up to three sources of uncertainty has been incorporated into an on line semi-supervised software on the SAFE FOOD PACKAGING PORTAL (INRA 2008). It generates all proposed diagrams in less than 3 minutes so that the overall decision tree can be easily integrated along with the process of identification and quantification of substances and along with the audit of the provider.

Apart from the decision tool concept, this work brought two important insights for both compliance testing and future sanitary survey. The migration of large additives such as antioxidants is mainly controlled by the resistance of material to diffusion. This low effect of partitioning is exacerbated by their higher chemical affinity for food simulant consisting in much smaller molecules. As an example of consequence, long time contacts and heating should lead to higher contamination of food products by large additives than by smaller ones even if they had a similar chemical composition. As this description neglects a possible

hydrolysis of additives, a dedicated experimental verification is encouraged. Finally, the results highlighted that the crude assumptions recommended in the current “Practical Guide” (2003) for modeling, based mainly on simulant D and strong overestimates of diffusion coefficients, failed to deserve the demonstration of compliance for intentionally added substances in most of tested cases. As modeling combined with fast deformation techniques appear to be the mainly independent approach to audit the compliance, further extension of this work to other polymers and multilayer materials is highly desirable.

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Table I. Transition and overall probabilities of the decision tree plotted in Figure 1. The final probability to demonstrate the compliance is denoted $p_{\text{compliance}}$. The values obtained with the current methodologies used at LNE (Laboratoire National de métrologie et d'Essais) and the expected values with the new proposed paradigm are compared.

	Notations	Current state at LNE†	Expected value with the new methodology‡
Transition probabilities	a	5%	50%
	b	50%	75%
	c	10%	80%
	d_{SML}	90%	90%
	d_{MIC}	50%	50%
Overall probabilities	$p_1 = a$	5%	50%
	$p_{2,\text{SML}} = a \cdot b$	2.5%	37.5%
	$p_{3,\text{SML}} = a \cdot b \cdot c$	0.25%	30%
	$p_{4,\text{SML}} = a \cdot b \cdot c \cdot d_{\text{SML}}$	0.20%	27%
	$p_{2,\text{MIC}} = a \cdot (1-b)$	2.5%	12.5%
	$p_{3,\text{MIC}} = a \cdot (1-b) \cdot c$	0.25%	10%
	$p_{4,\text{MIC}} = a \cdot (1-b) \cdot c \cdot d_{\text{MIC}}$	0.13%	5%
	$P_{\text{compliance}} = p_{4,\text{SML}} + p_{4,\text{MIC}}$	0.33%	32%

†The values were in particular inferred from the number and type of compliance requests received by LNE during the last five years.

‡The values were derived from blind samples tested during the project RA05.22

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Table II. List of tested substances.

Category	Code	Chemical name	Function	CAS number	M (g·mol ⁻¹)	SML (mg·kg ⁻¹)	Chemical structure
Plastic additives	Irganox 1076	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate	radical scavenger	2082-79-3	530	6	
	Irgafos 168	Phosphorous acid, tris(2,4-di-tert-butylphenyl) ester	hydroperoxide decomposer	31570-04-4	647	60	
	Erucamide	Cis-13-docosenoamide	slip agent	00112-84-5	337	60	
	BHT	Butylated hydroxytoluene	radical scavenger	000128-37-0	220	3	
	Irganox 1330	1,3,5-Trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene	radical scavenger	01709-70-2	774	60	

Category	Code	Chemical name	Function	CAS number	M (g·mol ⁻¹)	SML (mg·kg ⁻¹)	Chemical structure
	Irganox 3114	1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	radical scavenger	27676-62-6	784	5
Low molecular weight contaminants	2-ITX	2-(1-methylethyl)-9H-Thioxanthen-9-one	Printing ink photoinitiator	5495-84-1	254	10 ^{-2‡}
	DPM	diphenylmethane	reference†	101-81-5	168	10 ^{-2‡}

† experimental partition coefficient between HDPE and ethanol is available (Baner *et al.*, 1991).

‡ threshold value corresponding to the migration of an authorized below the detection level through a functional barrier as described in article 10 of directive 2007/19/EC (EC, 2007).

Table III. List of inputs used to predict the migration from a polyolefin to a 50:50 v/v water-ethanol simulant.

PARAMETER	Homologous migrant [†] Polymer notation (unit)	Low molecular weight contaminants		Plastic additives		
		2-ITX not available LDPE ^{††}	DPM not available LDPE ^{††}	BHT not available HDPE ^{†††}	Irganox 1330 BHT (3) HDPE ^{†††}	Irganox 3114 BHT (3) HDPE ^{†††}
Thickness	l_P (μm)	50	50	200	200	200
Volume dilution ratio	$L_{F/P}$ (-)	360	360	50	50	50
Biot mass number	Bi (-)	10 ³	10 ³	10 ³	10 ³	10 ³
Contact Time	t (days)	90	90	10	10	10
Temperature	(°C)	4	4	40	40	40
Likely initial concentration ^a	$\bar{C}_{i,P}^0$ ^a (mg·kg ⁻¹)	100 ± 10	100 ± 10	10 ³ ± 100	10 ³ ± 100	10 ³ ± 100
Conservative initial concentration ^b	$(\bar{C}_{i,P}^0)^+$ ^b (mg·kg ⁻¹)	300	300	3·10 ³	3·10 ³	3·10 ³
Likely diffusion coefficient ^c	$\bar{D}_{i,P}$ ^c (m ² ·s ⁻¹)	8.4·10 ⁻¹⁶ [7.6·10 ⁻¹⁶ 9.2·10 ⁻¹⁶]	7.3·10 ⁻¹⁴ [6.7·10 ⁻¹⁴ 8.0·10 ⁻¹⁴]	2.7·10 ⁻¹³ [2.5·10 ⁻¹³ 2.9·10 ⁻¹³]	1.6·10 ⁻¹⁵ [1.5·10 ⁻¹⁵ 1.8·10 ⁻¹⁵]	1.6·10 ⁻¹⁵ [1.5·10 ⁻¹⁵ 1.8·10 ⁻¹⁵]
Conservative diffusion coefficient ^d	$D_{i,P}^+$ ^d (m ² ·s ⁻¹)	3.9·10 ⁻¹⁴	1.1·10 ⁻¹³	4.4·10 ⁻¹²	3.6·10 ⁻¹⁴	3.4·10 ⁻¹⁴
Likely partition coefficient ^e	$\bar{K}_{i,F/P}$ (-)	1.4·10 ⁻⁹ [3.7·10 ⁻¹⁰ 5.1·10 ⁻⁹]	1.2·10 ⁻⁴ [3.4·10 ⁻⁵ 4.6·10 ⁻⁴]	2.1·10 ⁻⁴ [5.7·10 ⁻⁵ 7.7·10 ⁻⁴]	2.9 [0.77 10]	0.013 [3.5·10 ⁻³ 0.048]
Conservative partition coefficient	$K_{i,F/P}^+$ (-)	10 ³	10 ³	10 ³	10 ³	10 ³

[†] molecule which gives a similar IR absorption spectrum with a molar ratio indicated between brackets.
^{††} density = 0.899, crystallinity = 30%; ^{†††} density = 0.959, crystallinity = 70%.
^a chosen to fit real concentrations for a similar packaging material.
^b three times the likely value (matched the maximal recommended values for Irganox 1330 and Irganox 3114).
^c robust estimate according from Vitrac *et al.* (2006) and available on the SAFE FOOD PACKAGING PORTAL (INRA, 2008), 95% confidence intervals in brackets include the overall uncertainty on $D_{i,P}$ and its activation energy for this class of substance.
^d from the overestimate model described in Beygley *et al.* (2005).
^e calculated from the generalize Flory-Huggins approach described by Gillet *et al.* (2009c) for water-ethanol mixtures, all inputs required from thermodynamical and Molecular simulations are listed in Table 3. 95% confidence intervals based on a sensitivity analysis are indicated between brackets.

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630 **Table IV.** Combination of input values associated to each scenario. The index i in scenarios 1..8 corresponds to an identified substance, whereas
631 the index h in scenarios 9..10 corresponds to an homologous molecule (BHT for antioxidants) with a similar mid-infrared vibrational spectrum
632 (Gillet *et al.*, 2009a).

Scenario	$C_{i,P}^0$ value	$K_{i,F/P}$ value	$D_{i,P}$ value
1	$\overline{C}_{i,P}^0$	$\overline{K}_{i,F/P}$	$\overline{D}_{i,P}$
2	$(C_{i,P}^0)^+$	$\overline{K}_{i,F/P}$	$\overline{D}_{i,P}$
3	$\overline{C}_{i,P}^0$	$K_{i,F/P}^+$	$\overline{D}_{i,P}$
4	$\overline{C}_{i,P}^0$	$\overline{K}_{i,F/P}$	$D_{i,P}^+$
5	$(C_{i,P}^0)^+$	$K_{i,F/P}^+$	$\overline{D}_{i,P}$
6	$(C_{i,P}^0)^+$	$\overline{K}_{i,F/P}$	$D_{i,P}^+$
7	$\overline{C}_{i,P}^0$	$K_{i,F/P}^+$	$D_{i,P}^+$
8	$(C_{i,P}^0)^+$	$K_{i,F/P}^+$	$D_{i,P}^+$
9	$\overline{C}_{h,P}^0 \dagger$	$\overline{K}_{h,F/P}$	$\overline{D}_{h,P}$
10	$(C_{h,P}^0)^+ \ddagger$	$\overline{K}_{h,F/P}$	$\overline{D}_{h,P}$

633 $\dagger$ 852 mg·kg⁻¹ in BHT to match an equivalent concentration in BHT patterns included in Irganox 1330 and Irganox 3114. $\ddagger$ 3000 mg·kg⁻¹.

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Figure 1: Decision diagram to demonstrate the compliance of plastic materials according to article 8 of directive 2002/72/EC. Current and modified transition probabilities of acceptance are gathered in table 1. Additional improvements via iterative modeling appeared as dotted lines.

Figure 2. Influence diagram relating all ten scenarios involved in the assessment of compliance when migration modeling and deformation experiments are combined together.

Figure 3. Estimated concentrations in HDPE, $C_{i,P}^0$, of three additives against the number of extraction steps. All concentrations were normalized according the value after 4 extractions and denoted $C_{i,P}^0$.

Figure 4. Dimensionless migration kinetics of BHT, Irganox 1330 and Irganox 3114 corresponding to likely input values in Table III: a) kinetics on a log-log scale, b) kinetics against the square root of time. Dimensionless contact time, Fo_{10} , corresponding for each migrant to contact times of 10 days are depicted by dashed lines.

Figure 5. Isocontours of $10^3 \cdot C_{i,F}^{(Fo)} / C_{i,P}^0$ against Fo and $K_{i,F/P}$ for a,c,e) $L_{F/P}=50$) and b,d,f) $L_{F/P}=83$: a-b) BHT, c-d) Irganox 3114, e-f) Irganox 1330. Scenarios 1..8 are also represented as α (scenarios 1 and 2), β (scenarios 3 and 5), γ (scenarios 4 and 6), δ (scenarios 7 and 8).

Figure 6. Sensitivity diagram of $C_{i,F}^{(Fo)}$ against all unknowns: a) i =BHT, b) i =Irganox 3114, c) i =Irganox 1330, d) i =2-ITX, e) i =DPM. Error bars represent 95% confidence intervals on

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estimates. The limit of concern appears as a dashed line. Scenarios including $\bar{C}_{i,p}^0$ and $(C_{i,p}^0)^+$ are plotted as circles and squares respectively.

Figure 7. Decision diagrams expressed as ordered *MIC* values for scenarios 1..8: a) *i*=BHT, b) *i*=Irganox 3114, c) *i*=Irganox 1330, d) *i*=2-ITX, e) *i*=DPM.

Figure 8. Decision diagram when Irganox 1330 or Irganox 3114 is replaced by a similar concentration in BHT patterns, $\hat{C}_{BHT,F}^{Fo_{10}}$, with the properties of BHT (see Table 2). Scenarios 9 and 10 are calculated with $\bar{D}_{BHT,P}$ and $\bar{K}_{BHT,F/P}$ whereas scenarios 9' and 10' are equivalent scenarios calculated with $D_{BHT,P}^+$ and $K_{BHT,F/P}^+$. The decision is taken by comparing $\hat{C}_{BHT,F}^{Fo_{10}} / SML_{BHT}$ with one. The corresponding limit for the real additives is also depicted.

Figure 9. Decision diagrams expressed as minimum path lengths in the influence diagram depicted in Figure 1 (the decision process is started with scenario 10): a) *i*=BHT, b) *i*=Irganox 3114, c) *i*=Irganox 1330, d) *i*=2-ITX, e) *i*=DPM.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5
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Fig. 7

Fig. 8

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